REMARKS

A check for the requisite fees for a three-month extension of time and RCE filing accompanies this response. Any fees that may be due in connection with this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition. The RCE form reflects a change in correspondence address for the undersigned.

Claims 26-29, 31, 32, 34-37, 40, 42, 44-46, 48-54, 57 and 65-97 are pending in this application. Claims 29, 31, 40, 86 and 87 are amended herein and claims 96 and 97 are added. are amended herein to render it clear that the methods are designed to inhibit activation proliferation or migration of immune cells and/or to prepare conjugates for this purpose. Claims 96 and 97, which are added, find basis in claims 86 and 87.

A copy of references Shuh et al. (2003) Eur J. Immunol. 33:3080-3090 and Bruhl *et al.*, (2001) J. Immunol. 166:2420-2426, supporting arguments below are attached. These references demonstrate that a chemokine-toxin (RANTES fused to the truncated form of the bacterial toxin Pseudomonas exotoxin A (RANTES-PE38) eradicates chemokine receptor 5 (CCR5) bearing cells including HIV infected leukocytes and leukocytes derived from the synovial fluid derived from patients with arthritis (Bruhl et al., 2001 J. Immunol. 166: 2420-6). Shuh *et al.*, shows that this conjugate containing RANTES linked to Pseudomonas exotoxin (PE) is effective for treatment of asthma and hence has activity. Using *in vitro* vitro models and an *in vivo* mouse model, Shuh *et al.* demonstrates that the RANTES-PE38 conjugate retains the functionality of RANTES to bind to its receptors (CCR5, CCR3 and CCR1) and internalize the linked toxin. Hence, as described in the application, one of skill in the art can prepare conjugates that function as claimed and described.

THE REJECTION OF CLAIMS 26 29, 31, 32, 34 38, 40, 42. 4446. 48 54. 52, 65 and 91 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 26, 29, 31, 32, 34 38, 40, 42. 4446. 48 54. 52, 65 and 91 are rejected under 35 U.S.C. § 112, first paragraph, as being broader than the enabling disclosure for reasons discussed in turn below. The Examiner's arguments are repeated and each is rebutted in turn below. This rejection is respectfully traversed.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of ' 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971) (emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). There is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of

the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without undue experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. Id. 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against the claimed subject matter. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

Analysis and rebuttal

The analyses and arguments in the previous responses of record are incorporated by reference herein.

1. The claims

The independent claims are as follows:

Claims 29 and 72

Claim 29 is directed to a a method for inhibiting activation, proliferation or migration of immune effector cells by administering a conjugate to an animal whereby activation,

proliferation, migration of the immune effector cells is inhibited. The conjugate contains a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to a chemokine receptor on immune effector cells and facilitate internalization of the conjugate; the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell; the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell; and the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 72 is directed to a method for inhibiting activation, proliferation or migration of immune cells by contacting immune cells with a conjugate that contains a toxin or a portion thereof and a chemokine receptor targeting agent, whereby activation, proliferation, migration of the immune cells is inhibited. The chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 40

Claim 40 is directed to a method for inhibiting the proliferation, migration or activity of secondary tissue damage-promoting inflammatory cells by administering an effective amount of a therapeutic agent that inhibits the proliferation, migration or activity of secondary tissue damage-promoting inflammatory cells. The therapeutic agent is a conjugate that contains a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or activity of the secondary tissue damage-promoting cells.

Claim 86

Claim 86 is directed to a method for preparing a compound for treating a disease or disorder involving activated immune cells an inflammatory response, by:

identifying immune cells that are activated in the disease or disorder;

identifying chemokine receptors expressed on the cells;

preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells.

Dependent claims for each independent claim specify particulars regarding the conjugates and methods.

Hence the claims are directed to methods for targeting cells immune cells, including effector immune cells and secondary tissue damage-promoting cells, and to methods of inhibiting their activation, migration or proliferation. Claim 86 is directed to a methods for preparing the conjugates. The claims have been amended to clarify that the methods are not per se methods of treatment of particular diseases, but are methods of targeting or inhibiting activation. proliferation or migration of immune cells that are involved in the inflammatory response. By virtue of targeting such cells, the inflammatory processes are altered and conditions, such as secondary tissue damage, in which such processes and cells play a role are affected. It is noted that treatment as defined in the application is not synonymous with cure. The specification states that:

> As used herein. treatment means any manner in which the symptoms of a conditions, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.
>
> As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

Furthermore, as demonstrated in previous responses, the claims are based upon sound scientific reasoning and knowledge of those of skill in the art and bolstered by experimental evidence that demonstrates that the underlying science is correct. The responses and Declarations of record are incorporated by reference into this response.

As discussed below and acknowledged by the Examiner, the instant application discloses a "generic invention," and by virtue of applicant should be entitled to patent claims that cover such disclosure. The specification describes a selective treatment modality and compounds therefor for modulating inflammatory responses and thereby treating a variety of disorders in which an inflammatory response plays a role. The instant application teaches the

use of chemokine receptors, which are expressed on immune cells, as a target for delivery of agents to immune cells. As described in previous responses and in the application, the chemokine system, is intimately tied in to the immune system and specific chemokine receptors are expressed or elevated in certain diseases and disorders and in tissue damaging events and/or during the course of development of disease or disorder. The specification provides numerous chemokine targeting agents, identifies the association of expression of particular chemokine receptors in particular disease states or conditions and teaches how to select a chemokine targeting agent for a particular condition.

As discussed previously, targeting of the inflammatory response as point of intervention is a not new; consequently, there is not need to show that all of diseases in which this response plays are role are treated. It already is known to those of skill in the art. In addition, the use of conjugates for targeted delivery of agents, such as toxins is known; hence there is no need to prove this. The targeted delivery of agents, such as toxins to immune cells is known; hence there should be no requirement to show that conjugates to such cells function as expected. .

Further, the Declarations of record demonstrate that the conjugates target the cells in recognized in vitro and in vivo models as described in the application. The **Shuh *et al.* and Bruhl *et al.*,** papers, provided herewith, demonstrate activity of another chemokine conjugate. As discussed below, it functions as described in the instant application. The Examiner has provided no basis to conclude that conjugates with other chemokines will not similarly target their receptors.

2. The Examiner urges that there is no demonstration that the conjugates will treat all pathologies. It is respectfully submitted that the Examiner incorrectly describes the claims and the teachings in the specification. As discussed above, the claims are directed to methods for targeting or inhibiting proliferation, migration or activation of immune cells is incorrect statement of the breadth of the claims and requisites for teaching how to make and use the conjugates.

Teachings in the specification

The specification details how to select a chemokine targeting agent (see, *e.g.*, Tables, 2, 3) , how to prepare conjugates, how to formulate the conjugates and administer them (see, e.g., Section F Formulation and Administration of the conjugates, page 142 et seq.). These

teachings are sufficient to satisfy the enablement requirement. The conjugates are composed of molecules of known function and, as shown in the DECLARATIONs will function according to the activities of the components. Accordingly, the specification has enabled the full scope of the claims. Those of skill in the art know that conjugates will target their respective receptors, that the immune system can be targeted and modulation of immune system cells has therapeutic effect on a wide variety of diseases and conditions. This application provides a new way of modulating the immune system.

. The Examiner states that:

> the application does not teach how to make and use what is claimed. The claims are drawn to a method of treating the underlying pathology of inflammatory responses. This method is performed *in vivo*. The breadth of these claims is excessive. The specification only discloses the use of OP98110 on a RIP assaynd on migrating target cells *in vitro* (Example 2). The specification does not provide any guidance or working examples of how to make and use toxin-chemokine conjugates for their claimed use *in vivo*.

Applicant respectfully disagrees. As discussed herein and in previous responses, the instant application teaches how to make the conjugates in great detail. The specification teaches and describes numerous chemokines and their binding profiles and exemplifies preparation of at least a dozen conjugates. In addition, the specification teaches how to select chemokine receptor targeting agents (see *e.g.*, Table 2 of record and also Table 3, below) and throughout the specification and how administer the conjugates (see, *e.g.*, pages 142 *et seq.)*

Furthermore, as discussed herein and previously, the instant claims are not directed to methods of treating the underlying pathology, but are directed to methods for targeting molecules to immune cells via chemokine receptors expressed thereon. Activated immune cells can involved in immunpathological processes that underly a variety of disorders. The Declarations of record, the specification and those of skill in the art, recognize that inhibiting activation, migration or proliferation of such cells can be used therapeutically to alleviate symptoms of a variety of disorders. The previous Declarations and responses have shown that there are known drugs that target such cells and that they are effective in alleviating symptoms of a variety of disorders. In addition, conjugates of targeting agents are known and in use.

The conjugates are designed to target and bind to receptors on immune cells and to be internalized there thereby. There are no assertions and no claims directed to treatment of all pathologies. The conjugates used in the methods contain chemokine targeting agents that bind to receptors on immune effector cells and are internalized thereby; there is no reason to provided that the instantly claimed conjugates do not bind to receptors on such cells. The consitutent molecules of the conjugates have known and defined activity; there is not evidence of record (and in fact the evidence of record contradicts such finding) that the conjugate will not retain the activity of the constituent moelcules (i.e., chemokine receptor binding and internalization and, where the targeted agent is a toxin, toxicity).

As discussed in previous responses and herein, the use of conjugates for targeting to receptors well-accepted and well known; the activity of the components are documented and also described in the application.. This application provides a class of conjugates and a conceptually new treatment modality - the use of chemokine receptors for targeting to activated leukocytes. Targeting activated leukocytes is known, and the use of conjugates per se to target agents to cells via cell surface receptors is known. Activated leukocytes are involved in a variety of pathologies; hence modulation of the levels of leukocytes will interfere with are modulate a variety of pathologies.

As described in the application in great detail and summarized in the previous response, the activation, migration and proliferation of immune effect or cells, particularly leukocytes, are the hallmark of a vast number of immunomodulatory diseases. These cells are responsible for the production of inflammatory mediators and toxic molecules (such as cytokines, reactive oxygen species, metalloproteinases and cytotoxins) that are essential for the host immune defense against invading pathogens, such as bacteria and viruses. Inappropriate triggering, disregulation or over-activation of the immune response is responsible for the damage to normal host tissue witnessed in leukocyte-mediated diseases such as arthritis, multiple sclerosis, and pulmonary diseases. Leukocyte-mediated diseases also include trauma (e.g. spinal cord injury) and cancers and others. In the latter, leukocytes exert tumorigenic effects by nourishing the cancer directly or indirectly (by directing angiogenesis), by supplying chemokines and growth factors, and aiding metastasis by supplying various extracellular proteases.

Leukocytes are the mediators of diseases that can have combinations of allergic, autoimmune, angiogenic, inflammatory, and tumorigenic components. It must be noted that leukocytes are not necessarily the trigger of disease (which may be viral , bacterial, allergen, aberrant gene expression, trauma etc B initiated) but the excess immune (leukocyte) response is responsible for disease manifestation and progression.

This application provides an avenue of the therapeutic intervention that exploits this common underlying response (termed an underlying pathological response in the claims). Selection of this pathway for therapeutic intervention is not new (see discussion below); what is new in this application is the mode of intervention and the conjugates designed therefor; it is known that if activated leukocytes are modulated, that the inflammatory response is modulated.

It also known that the inflammatory response plays are role in a variety of diseases. Consequently, there is no need to demonstrate in this application that modulation of the levels of activated leukocytes is effective for disease treatment. This is known. For example, corticosteroids are known to affect the inflammatory response. Corticosteroids are administered for treatment of the diseases for which the instantly claimed conjugates are intended. Such diseases include, autoimmune disease, cancer therapy, allergies, MS, inflammatory bowel disease, Chron's disease, viral diseases (i.e., viral eye infections).

Similarly, the conjugates, which are designed to bind to and target activated immune cells, which are the hallmark of inflammatory responses, can be used to treat a variety of diseases. The chemokines, however, provide a different modality of intervention and provide a way to specifically target activated leukocytes associated with a disease state. The instant application provides conjugates that are targeted to specific chemokine receptors as therapeutic agents that target the common underlying response (see, e.g., Arimilli et al. (2000) Immunological Rev. 177:43-51).

The instant inventors, however, recognized that chemokines play an intimate role in these varied diseases, and, as described in the application, provide a large repertoire of molecules that interact with an array of receptors. It is the instant inventors who have identified chemokine receptors as ideal targets for delivery of therapeutics, such as toxins, to cells that participate in an underlying common response. The **claimed methods are for inhibiting proliferation, migration or activation of cells involved in such response.**

Knowing the mode of intervention, the use of chemokines as targeting agents as described herein, one of skill in the art will recognize by virtue of knowledge in the art and the disclosure in the application, that the conjugates provided herein provide a means for treatment of any disease in which in inappropriate triggering, disregulation or over-activation of the immune response is involved.

The instant applicant is not claiming the concept that these diseases are linked by an underlying pathology, such concept is recognized by those of skill in the art, but is providing a new avenue of treatment that exploits the common underlying pathology. As noted above an previously, this common underlying pathology is known to be appropriate for intervention in diseases involving an inflammatory response.

For example, U.S. Patent No. 5,750, 565 is directed to the use of tetrahydrofurans tetrahydrothiophenes, pyrrolidines and cyclopentanes to treat inflammatory disorders by inhibiting the enzyme 5-lipoxygenase. The patent states:

> These compounds in general reduce the chemotaxis and respiratory burst leading to the formation of damaging oxygen radicals of polymorphonuclear leukocytes during an inflammatory or immune response. The compounds exhibit this biological activity by inhibiting the enzyme 5-lipoxygenase.

And later:

> Examples of immune, allergic and cardiovascular disorders include general inflammation, cardiovascular disorders including hypertension, skeletal-muscular disorders, osteoarthritis, gout, asthma, lung edema, adult respiratory distress syndrome, pain, aggregation of platelets, shock, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, autoimmune uveitis, allergic encephalomyelitis, systemic lupus erythematosus, acute necrotizing hemorrhagic encephalopathy, idiopathic thrombocytopenia, polychondritis, chronic active hepatitis, idiopathic sprue, Crohn's disease, Graves ophthalmopathy, primary biliary cirrhosis, uveitis posterior, interstitial lung fibrosis; allergic asthma; and inappropriate allergic responses to environmental stimuli such as poison ivy, pollen, insect stings and certain foods, including atopic dermatitis and contact dermatitis.

The claims in that patent recite:

> a method for the treatment of inflammatory disorders using their compounds which include cardiovascular disorders, asthma, psoriasis, adult respiratory distress syndrome, atopic dermatitis, and contact dermatitis.

U.S. Patent No. 6,140,338, an issued patent, with a filing date subsequent to the instant application's effective filing date states that:

> Chemokines are polypeptidic leukocytic migration factors having molecular weights of about 10,000, and at least 21 types of peptide families having similar structures have been found. Further, at least 7 types of the chemokine receptors to which chemokines bind exist on leukocyte, and the receptors are considered to play an important role by means of selective migration and activation of leukocyte in many inflammatory diseases [Trends in Pharmacological Sciences, 17, 209-213 (1996)]. Accordingly, substances which specifically inhibit binding of chemokines to the chemokine receptors are considered to suppress the selective migration and activation of leukocyte and thus be useful as pharmaceutical drugs for prevention or treatment of e.g. acute or chronic inflammatory diseases such as septicemia, pneumonia, arthritis or allergic diseases, cancer, ischemic reflow disorder, arteriosclerosis, or rejection symptoms after organ transplantation operation. Further, in recent years, the chemokine receptors have been identified to be receptors on target cells, which are important for AIDS virus (HIV) to infect to the target cells [Nature, 381, 661-666 (1996); Nature, 381, 667-673 (1996); Cell, 85, 1149-1158 (1996)].

The claims in that patent are directed to a method of treating a disease or conditions including, acute inflammatory disease, chronic inflammatory disease, chronic inflammatory disease, acquired immune deficiency syndrome, ischemic reflux disorders, and arteriosclerosis; septicemia, pneumonia, or arthritis; an allergy or rejection symptoms after an organ transplantation operation by suppressing selective migration and activation of leukocytes. **Hence, as taught in the instant application, suppression of migration and activation of leukocytes can effectively treat such diseases.**

Subsequent to the filing of the instant application, others have reached the conclusion that chemokines play a role in a diverse set of disorders by virtue of their role as causing activation, proliferation and/or migration of immune cells (see, e.g., Proudfoot et al. (2000) Immunology Rev. 177:246-256; Segerer et al. (2000) J Am Soc. Nephrol 11:152-176; Armilli et al. (2000) Immunolog. Rev. 177: 43-51; Juang et al. (2000) Immunolog. Rev. 177:52-67; Gutierrez-Ramos et al. (2000) Immunolog. Rev. 177:31-42; Gerard et al. (2001) Nature Immunol. 2:108-115). These references, which are subsequent to the instant application, are

provided not to establish enablement, but to demonstrate operativeness and to evidence confirmation of what is taught in the instant application.

In addition, subsequent publications have demonstrated that antagonizing chemokine activity (a different modality from the instantly claimed methods in which the cells involved are targeted) is effective in treating a variety of disorders that share the underlying pathology (see, e.g., Ghirnikar *et al.*. (2000) J. Neuroscience Res. 59:63-73). See, also, Shuh *et al.*, which is provided herewith, which demonstrates activity of a RANTES-PE conjugate for inhibition of leukocytes and thereby treatment of disease.

Subsequent references establish in recognized animal models that depletion of immune cells is an effective treatment (see, *e.g.*, Popovich *et al.* (1999) J. Experimental Neurol. 158:351-365; Hoover *et al.* (2000) Immunol. 101:501-511) for disorders, such as spinal cord injury, pulmonary immune fibrosis and others. Other references establish the role of immune cells in the pathology of a variety of disorders (discussed in detail in the application and prior response; see, also Huitinga *et al.* (1990) J. Exp. Med. 172:1025-1033; Hoover *et al.* (2000) Immunol. 101:501-511).

A recent publication of the subject matter of this application by the inventor that describes (as does the instant application) the role immune cells, particularly of leukocytes, in disease manifestation and progression of the seemingly unrelated disorders and diseases recited in the claims (see, McDonald et al. (2001) IDrugs 4:427-442). It is the proliferation, activation and migration of the immune cells that are targeted by the conjugates. By inhibiting proliferation, activation and/or migration thereof, a variety of disorders can be treated. In virtually all diseases, the treatment, inhibition of proliferation, activation and migration of the immune cells is the same, the difference will be the disease manifested by the treated subject.

Depletion of cells is recognized to be an effective for treatment of a variety of disorders. Eradicatinge cells involved in disease pathology (thereby eradicating the production of all noxious substances at once B and thus the apex of disease pathology) can be achieved by targeting immune cells, a route exploited by the instant methods (none have chosen the disease pathology provided in the instant application). As discussed previously, immune cell-depleting therapeutics are known to be effective for treatment of a variety of disorders (the status of each drug may be out-of-date since this chart was assembled):

Table 2. Examples of Leukocyte and Cancer Cell Depleting Therapeutics

Agent	Name	Company	Indication(s)
Monoclonal Antibody	ABX-CBL[3]	Abgenix	GVHD
	Anti-CD11a[3]	Xoma	Psoriasis Transplant Rejection
	Campath[3]	Millenium/Ilex	Leukemia (CLL) Multiple Sclerosis (MS)+
	Herceptin[1]	Genentech	Breast Cancer
	Rituxan[1]	IDEC/Genentech	Lymphoma (NHL)
	AntiCD20 +Rituxan		Arthritis*
Ligand-Toxin Fusion Protein	Bexxar[2]	Coulter/Corixa	Lymphoma (NHL)
	Genimmune[3]	Xoma	Leukemia Lymphoma Autoimmune Diseases
	Mylotarg[1]	AHP Corp.	Leukemia
	NBI 3001[3]	Neurocrine Biosciences	Glioma
	Ontak[1]	Ligand	Lymphoma (CTCL)
	Zevalin[2]	IDEC	Lymphoma (NHL)

1: FDA approved drug; 2: Awaiting FDA approval; 3: In late stage clinical trials.
Bexxar and Zevalin incorporate a radionucleotide as the toxin moiety.
*: A recent clinical trial showed that almost complete depletion of B-cells with using the combination therapy of anti-CD20 and Rituxan, was beneficial to patients with IgG RF committed rheumatoid arthritis – with no immunosupression. (Sustained Improvement in Rheumatoid Arthritis Following B-Lymphocyte Depletion., Edwards et al., (2000) Rheumatology [Oxford] 40:205-11).
+ Campath had dramatically increased the length of relapses (periods between attacks) and hence slowed disease progression in patients

Table 3. Leukocyte Depletion Studies

Indication	Leukocyte target	Agent	Model/Reference
Arthritis	Macrophages	Clodronate	Humans (Barrera et al., 2000) Mice (Van Lent et al., 1998)
Asthma	Eosinophils	Chemokine-toxin	Rats (Schu et al., 2003)
Colitis	Neutrophils	RP-3 mAb	Rats (Natsui et al., 1997)
Cutaneous Inflammation	Macrophages	Ligand-toxin	Mice (Thepen et al., 2000)

EAE/MS	Macrophages T-Lymphocytes	Clodronate Ligand-toxin	Rats (Huitinga et al.,1990) Rats (Weiner et al.,1996, 1998)
Emphysema	Macrophages	Mo-Mac mAb	Rats (Ofulue & Ko, 1999)
Glomerulonephritis	T-Lymphocytes Neutrophils	CD5 mAb CD44 mAb	Rats (Ikezumi et al., 2000) Rats (Takazoe et al., 2000)
Lung Eosinophilia	Eosinophils	CCR3 mAb	Mice (Grimaldi et al.,1999)
Lung Injury	Neutrophils	Granulotrap	Dogs (Tomizawa et al., 1999)
Myocarditis (EAM)	T-lymphocytes	CD2 mAb	Rats (Inomata et al., 2000)
SCI	Macrophages Macrophages Neutrophils	Colchicine Clodronate Nitrogen Mustard	Rats (Giulian et al., 1990) Rats (Popovich et al., 1999 Rats (Taoka et al., 1997)
TBI	Macrophages	Colchicine	Rats (Giulian et al., 1989,1993)
Uveitis	Macrophages	Clodronate	Rats (Pouvreau et al., 1998)

Abbreviation: mAb, monoclonal antibody; SCI, spinal cord injury; TBI, traumatic brain injury.

None, however, choose to intervene in the manner and with the agents claimed in this application. The instant application teaches and claims the use of the chemokine system of receptors and ligands to eradicate excess numbers of immune cells, such as activated leukocytes subtypes, which has heretofore not been taught or suggested. The application and DECLARATION of record establish using *in vitro* and *in vivo* animal models that the conjugates specifically target and eradicate immune cells.

Having demonstrated the specificity of the targeting and the ability to internalize targeted agents, one of skill in the art would recognize that any disease involving a proliferation, migration or activation of immune cells is susceptible to treatment with the conjugates. Applicant is providing conjugates that demonstrably target and inhibit the cells involved in the inflammatory response. The specification provides ample guidance and examples for treating a wide variety of diseases that share this common underlying cause and also provides detailed guidance for preparing pharmaceutical compositions

The specification provides a substantial amount of guidance for selecting particular chemokines for treating a particular disease and for effecting treatment thereof. For example, Table 1 in the application sets forth a list of representative chemokines associated with pathophysiological inflammatory responses, including secondary tissue damage, the

receptor(s) they bind to, and the cell types affected by each in humans. Table 2 in the application summarizes exemplary chemokine-receptor targeting agents (more than a dozen) for treatment of selected diseases and conditions; Table 3 provides the amino acid sequences of a variety of chemokines; Table 5 provides physical properties of a variety of chemokine targeting agents; Table 6 and the examples provide a dozen exemplary conjugates.

The specification also provides a detailed description of disease states associated with the inflammatory response and secondary tissue damage treatment of a provides ample guidance for the treatment of specific and classes of inflammatory disorders (see pages 151-160):

Exemplary disorders and conditions, in addition to spinal cord injury, include stroke, acute lung injury and acute respiratory distress syndrome (ARDS), Alzheimer's disease, Down's syndrome, inflammatory joint disease, HIV encephalitis, growth, neovascularization (angiogenesis) and metastases of several forms of cancer including, brain, breast, and lung cancers, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis and Crohn's disease, proliferative vitreoretinopathy and uveitis.

The specification describes at least five broad classes of disorders, including cancer, pulmonary diseases, viral infections, secondary tissue damage, inflammatory joint diseases and autoimmune disorders, and includes a description of at least 70 diseases that fall in one or more of these categories and describes how to select a targeting agent therefor. **Furthermore, treatment of the diseases involves administration of a conjugate for inhibiting activation, migration or proliferation of immune cells. As a consequence of such inhibition, and by virtue of selection of a subject with a particular disease, the subject is treated.**

In addition, those of skill in the art, as evidenced by the large body of literature directed to chemokines, can readily identify and select an appropriate chemokine or set thereof to use based upon the teachings and guidance in the specification, which teaches how to make conjugates and exemplifies how to test them for requisite activities. The conjugates target cells of the immune system involved in other diseases not a disorder of the immune system. The specification lists more than seventy such disorders, and describes, among other spinal cord injury, which is representative and exemplary, in detail. As stated on described on pages 152 et seq.:

> It has been found herein that the cell biology of more than seventy diseases and conditions, involving most organ systems, involved pathophysiological inflammatory responses in a manner similar to the cell biology of acute SCI. The following, non-exhaustive list, and the more detailed treatment of four clinical areas, are designed to illustrate some of the more important similarities. Exemplary disorders and conditions, in addition to spinal cord injury, include stroke, acute lung injury and acute respiratory distress syndrome (ARDS), Alzheimer's disease, Down's syndrome, inflammatory joint disease, HIV encephalitis, growth, neovascularization (angiogenesis) and metastases of several forms of cancer including, brain, breast, and lung cancers, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis and Crohn's disease, proliferative vitreoretinopathy and uveitis.

Administration of the conjugates herein target chemokine receptors on immune cells, which are involved in the such conditions. By administration of a conjugate to a subject with any of those diseases, the activation, proliferation or migration of immune cells will be inhibited. The particular immune cells can be targeted by selecting a particular chemokine receptor targeting agent **exactly as described in the instant application (see, *e.g.*, TABLE 2 and the text in the application).**

As described in the specification and in the DECLARATION, chemokine receptors are upregulated on cells, such as various leukocyte subtypes, that participate in such responses. Hence, the eradication or inhibition of such pathophysiologically upregulated cells will remove such cells. . As described, the chemokines and chemokine receptors constitute a large family, so that the chemokine can be selected in accord with the teachings in the application, based upon the cell and particular receptor specifically expressed on the cell. The specification provides exemplary lists of chemokines and identifies the cells upon which they are regulated and the disorders for which the chemokines could be used as targeting agents.

The DECLARATION and Examples provide data demonstrating the activity of at least two different conjugates that rely on chemokines (MCP-1 and SDF-1β) that have very different specificity and selectivity profiles, and shows that each is efficacious for a particular type of disorder. The Shuh *et al.* and Bruhl *et al.*. references demonstrate activity of another conjugate that relies on targeting to using RANTES, which as described in the specification targets eosinophils. The specification details which chemokines to select for a particular cell type and what disease will be affected (see, *e.g.*, TABLE 1 in the specification, which

describes cell type to which different chemokines bind, and TABLE 2 which describes exemplary ligands and the disease that will be affected.

As described in the specification, and supported by the data in the DECLARATION , specification, and Shuh *et al.*, and Bruhl *et al.*. papers, targeting delivery of toxins to chemokine-bearing cells provides a means for specific targeted delivery of agents, such as toxins. The in vitro data and in vivo xenograft mouse model data of record in this application shows that the conjugates are specifically targeted to activated cells and do not interact with quiescent cells.

Furthermore, the *in vivo* data presented evidences the relatively low toxicity of the conjugates, which all are designed to target activated immune effector cells. The data provided in the DECLARATION shows that even high doses of OPL98111 do not completely eradicate primary human monocytes in culture, since not all of them are in the activated state . lso, a massive (non-therapeu tic dose) IP dose (5 mg/kg) of OPL98111 had no apparent effect on the health of mice that were not sacrificed until over 3 weeks after treatment. Throughout the forty days of the course of experiment, mice receiving multiple doses of OPL98111 in two xenograft experiments exhibited no difference in health when compared to placebo treated mice. There is no reason to believe that any of the conjugates for use in the methods would behave differently, since the expression profiles of chemokine receptors are known.

3. Guidance

The Examiner states that an intended use of the claimed conjugates is to treat of a common underlying pathology that is shared by a variety of disorders and that these conjugates target immune effector cells involved in these pathologies. In other words, the claims are not drawn to treating all pathologies, but to modulating the activity of immune effector cells which are involved in a variety of pathological conditions. It is clear from the art that immune effector cells are involved in the pathology or etiology of numerous disorders. The specification does teach the artisan how to select, prepare and administer chemokine targeting agents for particular diseases and stages thereof.

It is unclear how the Examiner then concludes that "there is a lack of guidance and working examples of these conjugates regarding their intended use to treat the underlying pathology of inflammatory diseases. Therefore, the specification is not enabled."

As discussed above and previously and throughout this paper, the specification provides detailed guidance for selecting chemokine targeting agents for particular treatments, it provides detailed discussion of how to make conjugates as fusion proteins or chemical conjugates (section D, TABLES 2, 3 , the EXAMPOLES). The specification provides exemplary lists of chemokines and identifies the cells upon which they are regulated and the disorders for which the chemokines could be used as targeting agents (see, e.g., Tables 2, 3 and 6); the specification provides and teaches 12 different conjugates and provides descriptions of a numerous chemokine receptor targeting agents, including sequences thereof. Section F, starting at page 142 of the application provides a detailed description of the formulation and administration of pharmaceutical compositions containing the conjugates.

4. The Examiner continues:

> The specification simply provides a generic treatment modality for treating this underlying pathology and Applicants have provided no guidance or working examples of any species falling within this generic invention which has the intended desire of treating this underlying pathology. The specification does not teach how to practice the methods as claimed. While there is no requirement for disclosure of every species within a genus and Applicants are entitled to claims which are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which applicant has disclosed, Applicants have not enabled any species, especially not a representative number of species or examples using art-accepted models, in order to be entitled to the claimed genus of conjugates. As stands, this application, respectfully, represents a research project and an "invitation to experiment."

It is respectfully submitted that this is patently incorrect. It is correct that the specification provides a generic treatment modality, it is incorrect that the application fails to provide guidance and working examples of species falling "within this generic invention." As discussed, the specification provides (see section C) lists of chemokine targeting agents to employ in the conjugates, their particular specificities and how to select a chemokine, the cells that express chemokine receptors and the receptors to which each chemokine binds. The specification exemplifies with working examples, preparation of 12 conjugates and details specifics regarding a variety of others see, e.g., (Tables 3-6). Hence, the specification provides a plethora of details and working examples.

The Declarations and subsequent papers demonstrate that the conjugates have activity as described in the application; they bind to leukocytes that express the targeted receptors and are internalized thereby. As discussed above, the use of conjugates to target immune cells is known, so there is no reason to doubt that a conjugated targeted to a receptor using a targeting agent therefore will bind to the cell and act as predicted.

5. The Examiner cites Brenner v. Manson:

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct, 1966), the court held that:

"[u]nless and until a process is refined and developed to th[e] point - where specific benefit exists in currently available form - there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license, "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant respectfully notes that Brenner v. Manson is a case directed to the requisites for establishing utility under 35 U.S.C. § 101. Although the rejection is set forth under the guise of 35 U.S.C. §112, first paragraph, based upon reliance on Brenner v. Manson, the rejection appears to a rejection under 35 U.S.C. §101 for lack of operativess. It is inapt. In Brenner the claims at issue were directed to intermediates for making steroidal compounds for which there was no known utility. Brenner held that if the final product has no utility, an intermediate for making something that has no utility cannot have utility. The instant rejection is under 35 U.S.C. § 112, first paragraph, so Brenner is inapt with respect to this application. If the Examiner wishes to set forth such a rejection, then applicant will address it in detail.

Briefly, utility under 35 U.S.C. § 101 is a threshold requirement that can be met by demonstrating a use for any embodiments within the scope of a claim; there is no requirement for demonstrating that all embodiments within the scope of a claims have the same utility or a utility. The requisites for demonstrating utility under 35 U.S.C. '101 are satisfied in the instant case. Utility under 35 U.S.C. '101 is a minimal threshold issue that can be satisfied by a showing of any use. A small degree of utility is sufficient; an invention must be capable of performing some function that is recognized to be a patentable use, however small and whether or not it is better at such function than the prior art.

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" [guidelines, which address utility under 35 U.S.C. '101 and 35 U.S.C. '112, first paragraph] and an "Overview of Legal Precedent Governing the

Utility Requirement" [legal overview] to support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that: they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR '1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements. Further, the legal overview provided by the USPTO, in section II.B.1., explains that:

> [a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. '101. ..... To overcome this presumption, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see e.g., In re Langer 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible":

> To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not [e.g., if the assertion is "incredible in view of contemporary knowledge"], should the Examiner challenge the statement as not being credible.

Thus, the Examiner must accept as true any credible statement of utility made by the Appellant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion to have no reasonable scientific basis.

Further, as the Examiner also has acknowledged, there is no requirement that the utility of a pharmacologically active substance be proven by *in vivo* testing. In re Isaacs, 146 USPQ 193, 195 (CCPA 1965). "A standard in vitro test may be sufficient to demonstrate pharmacological activity of a compound." Bigham v. Godtfredsen, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also Nelson v. Bowler, 206 USPQ 881, 883 (CCPA 1980); and Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985).

With respect to pharmacological and therapeutic utilities, the legal overview provided by the USPTO, in section I.C., interprets Nelson v. Bowler as establishing the following:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to

> provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. ..... These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. [Emphasis added.]

The legal overview addresses the analysis of "credibility" of such utilities, in section II.B.2., as follows:

> Special care should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, or the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under '101. (Emphasis added)

Finally, the USPTO, in its legal overview, addresses some special considerations regarding asserted therapeutic or pharmacological utilities [Section III.] stating:

> The Federal courts have consistently reversed rejections by the Office asserting a lack of utility under '101 for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence supporting such a utility. In view of this, Examiners should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility.

Thus, where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility. Further, it is important to distinguish "pharmacological activity" from "therapeutic activity". Pharmacological activity refers, essentially, to any biological activity. For example, a compound that is demonstrated, via in vitro or in vivo testing, to affect a biological function such as blood flow, hormone binding, enzyme operation, etc. in vivo has pharmacological activity. As described above, the court, in Nelson v. Bowler, has stated that, "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public." Therefore, any pharmacological activity is practically useful.

In In re Brana 34 USPQ2d 1436, U.S. App. LEXIS 6362 (Fed. Cir. 1995) the Court has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the

first paragraph of '112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (WP 1971).

From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. (BNA) at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See <=21> In re Bundy, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (WP 1981). n17

The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, n18 do not question the usefulness of any compound as an anti¬tumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of in vivo murine tests relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. . . .

Taking these facts the nature of the invention and the PTO's proffered evidence into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of ' 112. In re Marzocchi, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370.

In articulation of the standard of utility under § 101, the Court In re Gaubert stated that "[T]he PTO must do more than merely question operability - it must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability." 187 USPQ 664, 666 (CCPA 1975). It is the Examiners initial burden to establish that those skilled in the art would question the objective truth of the asserted utility. It is only during the prosecution of applications in which "the nature of the asserted utility is so incredible as to create a strong presumption of inoperativeness [such as perpetual motion machines] that the issue should be raised. In the absence of any evidence or apparent reason why the claimed compounds do not possess the claimed utility, the alleged allegation of utility in the specification must be accepted as correct. Ex parte Heicklen, 16 USPQ2d 1463 (Bd. Pat. App. & Int'f. 1990); In re Kamal et al., 158 USPQ 320 (CCPA 1968).

Further, there is no requirement that the utility of a pharmacologically active substance must be proven by in vivo testing. In re Isaacs, 146 USPQ 193, 195 (CCPA 1965). In vitro tests can raise the presumption of in vivo

utility of the claimed compounds. "A standard in vitro test may be sufficient to demonstrate pharmacological activity of a compound." Bigham v. Godtfredsen, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also Nelson v. Bowley, 206 USPQ 881, 883 (CCPA 1980); and Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985).

In In re Hartop, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962), the Court held that, when one skilled in the art would accept a particular test or experiment as being reasonably predictable that a tested invention would operate as alleged or have the utility alleged, the burden on behalf of an applicant to show utility has been satisfied. The Court went on to note that Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration, and the Federal Trade Commission, not the U.S. Patent and Trademark Office.

Practical utility is a shorthand way of attributing value to the claimed subject matter, meaning that one of skill in the art can use a claimed discovery in a manner that provides some immediate benefit to the public. "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public" and "adequate proof of any such utility constitutes a showing of practical utility."Nelson v. Bowley, 206 USPQ 881, 883 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985):

[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public . . . since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility . . .the board erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use" Nelson v. Bowley, 206 USPQ 881, 883 (CCPA 1980).

The instant applicant has met this standard. One of skill in the art would recognize that the instantly claimed conjugates target chemokine receptors and are internalized in cells bearing such receptors. Delivery of a linked toxin will result in inhibition of such molecules. As the references of record demonstrate, delivery of a toxin to a targeted cells, such as one expressing FGF, or EGF receptors is recognized to support claims to anti-tumor therapy as are the use of conjugates to bind to and inhibit immune cells.

Further, the specification teaches how to make and use the conjugates; it describes the underlying scientific theory and describes how to select a chemokine for a particular use. The DECLARATIONs of record and the examples in the specification as acknowledged by the Examiner establish that the conjugates exhibit biological activity in recognized assays.

As discussed, all of the conjugates as claim bind to chemokine receptors on activated immune cells. As described in the specification and DECLARATION of record, the methods in the instant application involve targeting immune cells, which express chemokine receptors. The particular chemokine receptor expressed on the cells is a function of the progress of an inflammatory response and also the type of disorder. The specification provides detailed guidance regarding choice of a chemokine targeting agent and the expression of chemokine receptors in various disorders and also establishes that those of skill in the art are aware of such information.

The data provided in the specification and in the DECLARATIONs as well as the disclosure of the specification and information in the DECLARATIONs demonstrate that the conjugates do, as described in the specification target activated immune cells and, when the targeting agent is a toxin, inhibit proliferation of thereof. Once it is shown that several conjugates bind to the receptors as described, that is adequate to establish that conjugates that target chemokine receptors will bind thereto. There should be no need to show this with every different chemokine or receptor. The claimed methods are directed to targeting activated immune cells. Inhibiting the proliferation of the activated immune cells (and it is know in the art that treatment modalities that inhibit the inflammatory response) will "treat" i.e. reduce symptoms, of any disorder that involves undesirable proliferation of activated immune cells.

As stated above the case law and guidelines state that where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility. Further, it is important to distinguish "pharmacological activity" from "therapeutic activity". Pharmacological activity refers, essentially, to any biological activity. For example, a compound that is demonstrated, via in vitro or in vivo testing, to affect a biological function such as blood flow, hormone binding, enzyme operation, etc. in vivo has pharmacological activity. As described above, the court, in Nelson v. Bowler, has stated that, "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public." Therefore, any pharmacological activity is practically useful. In this instance, it is clear that a conjugate containing a chemokine receptor targeting agent and a targeted agent, such as a toxin, will have a biological activity,

since the chemokines are selected to have to the desired target and they will bind to their receptors. Thus, a biological utility adequate to support a utility has been demonstrated. Furthermore, this utility coupled with all of the teachings in the specification regarding how to select a chemokine targeting agent and how to administer it are more than adequate to demonstrate a utility for the instantly claimed conjugates. Therefore, Brenner v. Manson is inapt.

6. The Examiner urges:

> Applicants have an idea, but have not provided sufficient support to demonstrate that their idea is functional (i.e. enabled) in a true in vivo model system of inflammation. While it is true that Applicants have disclosed a general treatment modality (i.e. a generic invention) this general modality is not enabled, nor, again, have they provided a representative number of examples to enable their invention.

The instantly claimed methods are not directed to methods of treating inflammation, but are directed to methods targeting immune cells using conjugates that contain a chemokine receptor targeting agent. Applicant has demonstrated that the conjugates target cells that express chemokine receptors and are internalized thereby. Furthermore, as discussed and shown previously and herein, the effects of inhibiting immune cells are know; there is no need to requirement demonstrate that which is known. Those of skill in the art know that if immune cells, which are over expressed or activated in a disease are inhibited, that consequent effects are inhibited.

As discussed above, the specification provides a description of at least 50 chemokines and also describes preparation of other targeting agents and describes numerous targeting agents, providing sequences for at least a half dozen toxins and incorporates by reference countless others. Thus there are 1000's of conjugates described and provided . The specification details formulation and administration. There is no requirement in the U.S. Patent laws to provide clinical data . The specification details construction of the conjugates, selection of chemokine targeting agents and criteria therefore, exemplifies preparation of a dozen conjugates, and teaches how to make the conjugates, formulate and administer them. There is no requirement for any more disclosure. Furthermore, as discussed in detail herein, it has been demonstrated that the conjugates target the receptors, are internalized thereby and inhibit proliferation, migration or activation of immune effector cells as claimed.

The specification teaches how to make the conjugates (and nucleic acids for fusion proteins and expression thereof), exemplifies preparation of a dozen or more. The Declaration and subsequent papers of others (i.e., Shuh *et al.* and Bruhl *et al.*) demonstrate that the conjugates function as claimed in *in vitro* and in *in vivo* models.

7. The Examiner states:

> . . . the use of the xenograft model only demonstrates that 0PL98111 can be used to retard tumor growth relative to control animals and that it has an anti angiogenic effect. Furthermore, tumors are not inflammatory diseases and it is not clear how the treatment of tumors using the claimed conjugates can be enabling for the treatment of actual inflammatory diseases.. . . OPL98112, on the other and, was used in vivo and in vitro, but the in vivo results only show that the compound is not toxic. There is no data demonstrating that these compounds act as described in the claimed invention; that is by affecting [sic] the underling inflammation in any an all inflammatory diseases . . ..
>
> . . . it is not understood how the activated monocytes played a role in tumor progression. It is clear that the infiltration of monocytes into a tumor could inhibit tumor growth, but it is not clear how inhibition of these cells into a tumor can prevent tumor growth. Again, tumors are not inflammatory diseases and it is not clear how the treatment of tumors using the claimed conjugates can be enabling for the treatment of actual inflammatory diseases.

It is respectfully submitted that this is not correct. The DECLARATION shows inhibition of the migration and proliferation of immune effector cells The effect on the tumor is a consequence thereof.. The conjugates act to inhibit activation, migration or proliferation of immune effector cell as claimed. The data clearly demonstrates this as well as the specification and the science and knowledge of those of skill in the art. Tumors need nourishment and put out chemokines. Leukocyte infiltration ensues and the leukocytes provide nutrients for the tumor cells, chemoattractants for endothelial cells (angiogenesis) and more leukocytes. Therefore, macrophage (immune cell) migration and proliferation a part of the etiology of cancer and the data provided is pertinent. Those of skill in the art well-recognize the connection between activation of monocytes and tumor progression. Monocytes are immature macrophages and they are involved in inflammatory responses. The DECLARATION shows targeting and eradication of monocytes, which thereby impedes tumorigenesis.

Furthermore, there is no need to employ models of inflammatory disease. The application and data of record demonstrate that the conjugates bind to chemokine receptors on immune effector cells and are internalized thereby; this is what is claimed. This is shown

in the Declaration and as discussed above, and would be understood and accepted by those of skill in the art in view of the knowledge of those of skill in the art and the biology of the chemokine expression on immune effector cells.

The Examiner is not applying the appropriate standard. The application extensively describes how to make and use the conjugates. As demonstrated previously, Applicant is not the first to target immune cells, it is know to those of skill in the art that if one targets immune cells and kills them then concomitant effects will occur. The invention lies in the new target and approach. Applicant has demonstrated that the compounds disclosed in the application can distinguish between activated and quiescent cells and that activated, proliferating and migrating cells are targeted as claimed.

8. The Examiner urges:

> Applicants argue that, as taught in the Declaration and specification as tiled, the instant methods are based upon treatment of a common underlying pathology that is shared by a variety of disorders and that the methods target immune effector cells involved in these pathologies. In other words, the claims are not drawn to treating all pathologies, but to modulating the activity of immune effector cells which are involved in a variety of pathological conditions. Applicants argue that it is clear from the art that numerous different disorders share this common underlying pathology. Applicants argue that the specification does teach the artisan how to select, prepare and administer chemokine targeting agents for particular diseases and stages thereof and that the specification is presumed enabled even in the absence of working examples. Applicants further argue that the specification provides a generic treatment modality for treating this underlying pathology and there is no need for Applicants to disclose every species falling within this generic invention and the specification teaches how to practice the methods as claimed. Applicants argue that there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims [which] are commensurate in scope not only with what applicant has specifically exemplified, hut commensurate in scope with that which one of skiN in the art could obtain by virtue of that which applicant has disclosed." While this statement may he true, it does not summarize the present situation. The only data provided is that of a mouse xenograft model which demonstrates the effectiveness of these compounds on a tumor. This is not probative since it is not clear that the conjugates are affecting the underlying cause of tumor progression. as claimed in the present invention. Even, arguendo, this was an adequate example of the claimed methods, Applicants still have not provided a representative number of examples of treating inflammatory diseases using art accepted models. As stands, this application, respectfully, represents a research project and an invitation to experiment.

The treatment for all of the disorders is the same. One selects a chemokine receptor targeting agent and prepares a conjugate and administers it. The conjugate binds to the targeted receptors and is internalized thereby. If the linked agent is a toxin, the cells into which the conjugate is internalized are inhibited from migrating, proliferating or being activated. The specification details preparation of conjugates in great detal and exemplifies thousands. No experimentation is required. The Declaration shows that monocytes are inhibited. As discussed above, targeting of immune cells is not a new treatment target; the consequences of inhibiting proliferation, migration or activation of such cells are well known and documented. Those of skill in the art in light of the specification know that chemokines receptors are expressed on immune effector cells and can prepare conjugates that contain chemokine receptor targeting agents for delivery of linked agents, such as toxins and other metabolic inhibitors or other agents to such cells.

9 The Examiner states:

> The intention is to treat a disease or to treat the underlying pathology of the disease is a matter of semantics. It is not understood how Applicants are not treating the disease when they are treating the underlying pathology of a disease. Pages 151-160 of the specification teach a large list of inflammatory responses which Applicants state can be treated with the conjugates of the present invention. This includes Parkinson's disease, Alzheimer's disease, Down's syndrome. In fact, a "short" list of diseases which, according to Applicants, would be expected to be treated include such unrelated diseases as spinal cord injury, stroke, acute lung injury, acute respiratory distress syndrome, inflammatory joint diseases such as rheumatoid arthritis, HIV encephalitis, neovascularization, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis, Chron's disease, proliferative vitreoretinopathy and uveitis (see pages 152-153 of the specification). However, the specification does not teach the artisan how to select, prepare and administer chemokine targeting agents for particular diseases and stages thereof. The specification simply discloses the basic fact that "the artisan can select, prepare and administer chemokine targeting agents for particular diseases and stages thereof, (as seen in Tables 1-6 of the specification)," but does not provide any significant guidance of how to do so.

As noted above, treatment cannot be equated with cure; treatment is defined in the specification "any manner in which the symptoms of a conditions, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein. Amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to "any

lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition."

The instant application provides detailed guidance how to make the conjugates and how to formulate them and how to administer them. Further, the instant claims are directed to methods for targeting immune cells (and for preparing conjugates therefore). The specification details the types of immune cells that are activated in a particular disease state and teaches which chemokines are expressed. Treatment involves preparing the conjugates and administering them. There is detailed and significant guidance. The specification details how to make, how to formulate the conjugates and how to administer them. The specification as noted details specifics regarding selection of a particular chemokine for a particular disease. It is unclear what disclosure is lacking in teaching one of skill in the art how to pratice the claimed methods.

As discussed above, and as evidenced by the references previously provided and cited herein, the art recognizes that the inflammatory response is a mediator of symptoms of diseases such as "spinal cord injury, stroke, acute lung injury, acute respiratory distress syndrome, inflammatory joint diseases such as rheumatoid arthritis, HIV encephalitis, neovascularization, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis, Chron's disease, proliferative vitreoretinopathy and uveitis." There are treatments, such as the use of prednisone, that are known in the art that modulate the inflammatory response and that are employed to treat all of these diseases by targeting immune effector cells.

Also, the Tables above show that immune cell depletion strategies are employed for a treatment of a variety of diseases. Differences among the prior art (and even subsequent art) methods is the choice of the system with which to intervene. Some choose to intervene with inflammatory mediators (e.g., cytokines), others with angiogenic mediators (e.g., vascular endothelial growth factor). Others choose to intervene with leukocyte trafficking by exploiting the cell adhesion molecule systems (anti-selectins, anti-integrins, etc) or the chemokine system with receptor antagonists. Numerous leukocyte depletion studies using reagents to target specific leukocyte cell-sub-populations have shown beneficial effects in a wide variety of diseases in humans and animals (Tables above). This clearly demonstrates that the course of "unrelated diseases" (which they are not) can be influenced when a specific targeting agent is administered.

Hence, the methods of the instant application, which target and deliver conjugates to immune cells bearing chemokine receptors will be effective and also will influence the course of a variety of diseases. The instant methods effect treatment by targeting conjugates to the immune cells involved in the pathologies to deliver linked agents, such as toxins. The Declaration of record demonstrates this unequivocally.

The Examiner continues:

> If this information is so basic that the specification does not need to teach specific examples, then it is not clear why the specification does not provide examples of diseases (or underlying pathologies) being treated. It would seem to reason that if this information (i.e. treatment regimen) were, respectfully, as simple as the specification makes it appear, then showing that these diseases were actually treated would have been disclosed in the specification. It is apparent that, in fact, the ability to treat a disease by treating the underlying pathology is not as simple as the specification makes it appear. Inflammatory disease states are complex and Applicants are basically saying "here are known chemokines and cytokines. Use them however you can to treat any disease, and alter the regimen as you see fit when the stage of the disease progresses, but we are not going to tell you how to do this, since the chemokines and toxins are so well known." This is not adequate disclosure for enablement.

This is not what applicant is stating. The claims are directed to methods for targeting or preparing conjugates to immune cells for inhibiting proliferation, migration or activation thereof. This is adequately described and demonstrated. The listed diseases are those that involve activated immune cells as part of the pathology or etiology. General treatment strategies, such as administration of corticosteroids that target such cells and effect treatment of a wide variety of such diseases is well known. Prednisone is administered for treatment of virtually all of the listed diseases, including cancers, asthma, Chron's disease, viral infections and inflammatory disorders. The instant methods employ a different treatment modality.

As discussed above, the specification provides numerous Examples. Furthermore, the case law and the Patent Office Guidelines are very clear that there is no requirement in the U.S. Patent law to provide working examples nor to provide clinical data. Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration, and the Federal Trade Commission and not the U.S. Patent and Trademark Office, and it held the Patent office was wrong to insist on clinical trials In re Hartop, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962).

A specification is presumptively true; absence evidence of fraud the Examiner cannot doubt the veracity of the disclosure in the specification. As noted above, in In re Brana 34 USPQ2d 1436, U.S. App. LEXIS 6362 (Fed. Cir. 1995) the Court has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of '112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (WP 1971).

10. The Examiner urges:

> While Applicants may teach the chemokine system in detail, and an example of which receptors are present on certain cells at certain stages of disease progression, since this is known in the art, this "how to make and use the claimed invention" (i.e. conjugates) does not teach any more than the prior art discloses and this plethora of pages in the disclosure of how to make and use the conjugates is not a substitute for an enabling specification. Even though Applicants may suggest that specific chemokine-toxins would be effective in treating a wide array of conditions, this is merely a suggestion. This is a "wish to achieve", not an accomplishment. A person of ordinary skill in the art would not find it credible to treat all diseases, or the underlying pathology, based on the teachings of the specification. Given the wide range of disease and the complexity of disease states, along with a lack of guidance and working examples of functional conjugates, it would not have been predictable to one of ordinary skill in the art at the time of the present invention to have known which conjugates to use for a particular disease at a particular stage of the disease, or what the effects and side-effects of these conjugates would be. Applicants are basically using a "blanket" approach or a "magic principle" and leaving it up to the individual artisan to determine which conjugates will work under which conditions, under which diseases and under which stages of these diseases. In other words, respectfully, Applicants are leaving it up to the artisan to complete the required research for Applicants' desired patent. As taught by Benjamini et al (In Immunology: A short course, 3rd. ed. 1996) "Given the complexity of the immune response and its potential for inducing damage, it is self-evident that it must operate under carefully regulated conditions." Therefore, it would stand to reason that great care must be taken when choosing how and when to use the claimed conjugates to affect the immune system. The artisan cannot just assume that any conjugate will work as predicted under all circumstances, especially given the wide variety of circumstances (i.e. diseases). It is apparent that determining the effect of the conjugates on a patient would involve more than simply determining the toxicity of a particular conjugate, or believing that it is as simple as targeting a desired cell population with the expectation of no

> unwanted side-effects. In other words, the issue is, respectfully, more complex than stating "here are the known chemokines and cells to which they bind - the treatment, therefore, is commonplace."

As discussed above, the specification teaches how to prepare and administer the conjugates and provides a detailed discussion of a variety of diseases and indicates which chemokine receptor targeting agent should be selected for particular diseases. Further, the instant application teaches more than the prior art, the instant applicant teaches the use of the chemokine system and chemokine receptors expressed on immune cells, such as leukocytes (and other cells) as a point of therapeutic intervention. In all instances of treatment using the instantly claimed conjugates, the targets are activated leukocytes, which are known to be involved in these diseases. The conjugates act in the same manner for treatment of each disease - they bind to the targeted immune cells and are internalized thereby As detailed in the specification, different are activated in different diseases, and the chemokine system can be used to target the immune that will be activated in a particular disorder.

11. The Examiner concludes:

> Therefore, in summary, the breadth of the claims is excessive with regard to Applicants claiming methods for treating the underlying pathology of all inflammatory responses. The specification does not provide any guidance or working examples of how to make and use toxin chemokine conjugates for their claimed ruse in vivo, nor is it predictable to the artisan how to make and use the large number of conjugates available to treat the diverse types of diseases, or their underlying pathology, given what is taught in the specification. For these reasons, the Examiner maintains that undue experimentation would be required to practice the invention as claimed.

Applicant respectfully disagrees, as discussed above, the instant claims are not directed to methods of treating the underlying pathology for treating all inflammatory responses, but are directed to methods for inhibiting proliferation, migration or activation immune cells by targeting receptors expressed on such cells. As established and demonstrated above, acctivation, proliferation and migration of immune cells underlies the inflammatory response. As discussed in detail, the specification provides detailed guidance for selection of a chemokine targeting agent and describes which immune cells expres particular chemokine receptors. . Starting at page 119, the specification describes the chemokine receptors to target for particular immune cells, which are known to be activated, migrating and/or proliferating in a number of conditions including spinal cord injury (MIP-1α, MIP-1β), traumatic brain injury (MCP-1, RANTES, MIP-1β). Starting at page 151, the

specification describes which receptors and chemokines are upregulated particular disease states (i.e., IL-8, MCP-1, MCP-3, MIP-1α, RANTES and Eotaxin in inflammatory lung diseases), and in Table 2 sets forth a list of chemokines to use in conjugates and diseases to be treated therewith. Table 2 is reproduced herein:

TABLE 2
EXEMPLARY LIGAND(S) AND DISEASE TREATED

Ligand(s)	Disease/Condition
MCP-1 and 3, RANTES, *IP-10, IL-8, GROα*	Atherosclerosis and Restenosis
MCP-1 and 3, RANTES, *SDF-1β*	SCI, Traumatic Brain Injury, Stroke, AD
MCP-3 and 4, RANTES, *IP-10, Mig*	Multiple Sclerosis
Eotaxin, RANTES, MDC, *SDF-1β*	HIV
Eotaxin, MCP-1 and 4, MDC, *IL-8, ENA-78*	Inflammatory Bowel Diseases
MCP-3 and 4, RANTES, *IP-10, Mig, IL-8, ENA -78, GROα, I-TAC*	Inflammatory Joint Diseases (e.g., arthritis)
	Inflammatory Lung Diseases
MIP-1α, MIP-1β, MCP-1, 2, 3, 4, RANTES, *IP-10, IL-8, ENA-78*	Acute lung Injuries and Fibroses
Eotaxin, MCP-4, MDC	Allergic and Eosinophil-associated Diseases
MCP-1, *IL-8*	Inflammatory Eye Diseases
	Cancers
SDF-1β, IP-10, Mig, IL-8, ENA-78, GROα	Glioma
MCP-1, 3, and 4, RANTES, *SDF-1β*	Breast
MCP-1, *IL-8, ENA-78*	Lung

Italicized ligands are α or CXC chemokine family members the others are β or other chemokine family members. The ligands indicated can be used in combinations for the treatment of the indicated diseases. **In all instances, the targeted cells are activated, proliferating or migrating immune cells.**

The specification lists and provides numerous targeted agents and teaches how to make the conjugates. It is unclear how and why the Examiner concludes that there is no guidance or examples in the application. The application clearly teaches how to select particular chemokine targeting agents for treatment of a particular disease, provides

hundreds, if not thousands (more than a dozen each of chemokines, including identification of the disease to treat, and targeted agents exemplified and all permutations and combinations of these exemplified agents).

Therefore, in light of the extensive teachings and examples in the specification, the breadth of the claims, the knowledge of those of skill in the art (see discussion below as well regarding knowledge of those of skill in the art) and the high level of skill in the art, the application provides ample guidance sufficient to enable the skilled artisan to prepare and use the claimed conjugates for inhibiting migration, proliferation or activation of immune cells.

12. The Examiner urges:

> Applicants have an idea, but have not provided sufficient support to demonstrate that their idea is functional (i.e. enabled) in a true in vivo model system of inflammation. While it is true that Applicants have disclosed a general treatment modality (i.e. a generic invention) this general modality is not enabled, nor, again, have they provided a representative number of examples to enable their invention.

As discussed, this is incorrect. The specification provides thousands of conjugates that target chemokine receptors; describes how to prepare them and how to administer them. Applicant has demonstrated (also demonstrated by the attached references Shuh *et al.* and Bruhl *et al.*) that such conjugates target immune effector cells as claimed.

13. The Examiner continues:

> Furthermore, the specification does not teach the artisan how to select, prepare and administer chemokine targeting agents for particular diseases and stages thereof. The specification simply discloses the basic fact that the artisan can select, prepare and administer chemokine targeting agents for particular diseases and stages thereof (as seen in fables 1-6 of the specification), but does not provide any significant guidance of how to do so. If this information is so basic that the specification does not need
>
> to teach specific examples, then it is not clear why neither the specification, nor the Declarations, provide examples of diseases (or underlying pathologies) being treated. it would seem to reason that if this information (i.e. treatment regimen) were, respectfully, as simple and as predictable as the specification, Declarations and Applicants arguments make it appear, then showing that these diseases were actually treated would have been disclosed in the specification. It is apparent that, in fact, the ability to treat a disease by treating the underlying pathology is not as simple or as predictable as the specification and Declarations make it appear. Inflammatory disease states are complex and Applicants are basically saying here are known chemokines and cytokines. Use them however you can to treat any disease, and alter the regimen as you see fit when the stage of the disease progresses, but we are not going to tell

> you how to do this, since the chemokines and toxins are so well known. This is not adequate disclosure for enablement nor would this information make it predictable to the artisan how to make and use the conjugates to practice the claimed methods.

Again this is not a correct assessment. The claims only require that the conjugates target immune effector cells by preparing conjugate and administering it exactly as described in the specification. Furthermore, the Examiner is reminded that absent evidence of fraud the Examiner cannot doubt the veracity of a specification nor should the Examiner make any inferences regarding the presence or absence of clinical data in a specification. As discussed above, there is no requirement in the US Patent laws to provide any clinical data nor to include any working Examples in an application. Negative inferences cannot be drafwn from the absence of such Examples. In this instance, the specification provides thousands of conjugates, Exemplifies preparation of twelve and teaches how to prepare and administer them. There is no lack of exemplary disclosure.

14. The Examiner continues:

> Applicants argue that when one skilled in the art would accept a particular test or experiment as being reasonably predictable that a tested invention would operate as alleged or have a therapeutic effect as alleged, the burden on behalf of an applicant has been satisfied. While Applicants may teach the chemokine system in detail, and an example of which receptors are present on certain cells at certain stages of disease progression, since this is known in the art, this how to make and use the claimed invention (i.e. conjugates) does not teach any more than the prior art discloses and this plethora of pages in the disclosure of how to make and use the conjugates is not a substitute for an enabling specification.

Applicant respectfully disagrees. The application describes more than the prior art discloses; the application teaches how to make and use chemokine receptor targeting conjugates to exploit the chemokine receptor system and to thereby alter migration, activation or proliferation of immune effector cells. This is a considerable advance over the art. The specification details how to do this and how to exploit the chemokine receptor system.

15. The Examiner also states:

> A person of ordinary skill in the art would not find it credible to treat all diseases, or the underlying pathology, based on the teachings of the specification, nor would the artisan consider this approach predictable. A person of ordinary skill in the art would not find it credible to treat all diseases, or the underlying pathology, based on the teachings of the specification. Given the wide range of disease and the complexity of disease

> states, along with a lack of guidance and working examples of functional conjugates, it would not have been predictable to one of ordinary skill In the art at the time of the present invention to have known which conjugates to use for a particular disease at a particular stage of the disease, or what the effects and side-effects of these conjugates would be. Applicants are basically using a blanket approach or a magic principle and leaving it up to the individual artisan to determine which conjugates will work tinder which conditions, under which diseases and under which stages of these diseases. In other words, respectfully, Applicants are leaving it up to the artisan to complete the required research for Applicants' desired patent. As taught by Benjamin *et al.* (In Immunology:A short course, 3rd ed. 1996) "Given the complexity of the immune response and its potential for inducing damage, it is self-evident that it must operate under carefully regulated conditions." Therefore, it would stand to reason that great care must be taken when choosing how and when to use the claimed conjugates to affect the immune system. Thee artisan cannot just assume that any conjugate will work as predicted under all circumstances, especially given the wide variety of circumstances (i.e. diseases). It is apparent that determining the effect of the conjugates on a patient would involve more than simply determining the toxicity of a particular conjugate, or believing that it is as simple as targeting a desired cell population with the expectation of no unwanted side-effects. In other words, the issue is respectfully, more complex than stating here are the known chemokines and cells to which they bind - the treatment, therefore, is commonplace." Benjamin *et al.* is not being used as a new grounds of rejection, but simply to further support the Examiner's position that due to the complexity of the immune system, Applicants are not enabled for the scope of their claimed invention.

As discussed above, Applicant has demonsrated that the conjugates target immune effector cells and can inhibit their proliferation, activation or migration. As discussed above, targeting such cells is a known to be effective. Further, it is known that conjugates that bind to receptors on cells cells can be used to deliver agents to such cells *in vitro* and *in vivo*. What is new in this application is not the use of conjugates for diseases nor the targeting of immune effector cells. There is no evidence of record that one of skill in the art would have to any additional experimentation. As the papers of Shuh *et al.* and Bruhl *et al.*, demonstrate, the conjugates function exactly as described in the specification. The specification teaches the use of RANTES for targeting eosinophils and as shown, conjugates containing RANTES do so.

16. Utility

As discussed above, the Examiner appears to be making a utility rejection in the guise of an enablement rejection. Although the rejection is set forth under the guise of 35 U.S.C.

§112, first paragraph, based upon reliance on Brenner v. Manson, the rejection appears to a rejection under 35 U.S.C. §101 for lack of operativeness. The rejection is inapt.

In articulation of the standard of utility under § 101, the Court In re Gaubert stated that "[T]he PTO must do more than merely question operability - it must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability." 187 USPQ 664, 666 (CCPA 1975). It is the Examiners initial burden to establish that those skilled in the art would question the objective truth of the asserted utility.It is only during the prosecution of applications in which "the nature of the asserted utility is so incredible as to create a strong presumption of inoperativeness [such as perpetual motion machines] that the issue should be raised. In the absence of any evidence or apparent reason why the methods are not operable, the alleged allegation of utility in the specification must be accepted as correct. Ex parte Heicklen, 16 USPQ2d 1463 (Bd. Pat. App. & Int'f. 1990); In re Kamal et al., 158 USPQ 320 (CCPA 1968).

Further, there is no requirement that *in vivo* testing is required to demonstrate operability or utility. In re Isaacs, 146 USPQ 193, 195 (CCPA 1965). "A standard in vitro test may be sufficient to demonstrate pharmacological activity of a compound." Bigham v. Godtfredsen, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also Nelson v. Bowley, 206 USPQ 881, 883 (CCPA 1980); and Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985).

In In re Hartop, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962), the Court held that, when one skilled in the art would accept a particular test or experiment as being reasonably predictable that a tested invention would operate as alleged or have the utility alleged, the burden on behalf of an applicant to show utility has been satisfied. The Court went on to note that Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration, and the Federal Trade Commission, not the U.S. Patent and Trademark Office.

Practical utility is a shorthand way of attributing value to the claimed subject matter, meaning that one of skill in the art can use a claimed discovery in a manner that provides some immediate benefit to the public. "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public" and "adequate proof of any such utility constitutes a showing of practical utility."Nelson v. Bowley, 206 USPQ 881, 883 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985):

[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public . . . since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility . . .the board erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use" Nelson v. Bowley, 206 USPQ 881, 883 (CCPA 1980).

The Examiner respectfully is reminded that if a rejection on this ground is set forth, such Action cannot be made final.

Unduly limiting

The Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. It is unfair and unduly limiting to require applicant to limit the claims to three compounds, when the application clearly teaches how to make and use the full scope of the claimed products. The specification clearly places those of skill in the art in possession of a larger genus; the specification discloses a large number of chemokines and targeted agents and provides sequences or sources therefore; preparing the conjugates is routine. To so limit the claims not only is unfair, unduly limiting, it is contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims only to the a few of the exemplified species:

See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):
for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".

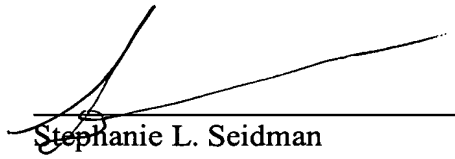
The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304. If applicant is required to limit the claims as required by the Examiner, then those of

skill in the art can by virtue of the teachings of this application select chemokines and prepare conjugates that inhibit proliferation, migration or activation of immune cells, thereby practicing what is disclosed in the application, but avoid infringing such limited claims. To permit that is simply not fair. The attached Shuh et al. and Bruhl et al., references, which describes making a chemokine-toxin conjugate for targeting to immune cells, demonstrates that this possibility is not remote, but already has occurred. The instant application teaches a modality and products for inhibiting proliferation, activation or migration of immune cells, abd having done so places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,



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